REMARKS

I. Status of the Claims. Upon entry of this Amendment, claims 14, 23, 24, 33, 35 and 38-57 are pending.

Claims 14, 23, 24, 33, 35 and 38-40 have been amended without prejudice or disclaimer to be directed to humanized free-end specific antibodies to Aβ. Support is found in the specification at, e.g., page 11, lines 24-28.

Support for new claims 41-57 is found throughout the specification, e.g., at page 23, lines 31-37 ("Antisenilin N1/5"); page 24, lines 8-13 ("Antisenilin C34/40"); page 13, lines 22-24 ("secretion of antisenilins into the cerebrospinal fluid, where Aβ peptides are present, promotes the formation of soluble antisenilin-Aβ complexes"); and Fig. 2 (showing amino acid sequences of the peptides in βAPP used for immunization to produce antisenilins).

By this Amendment, no new matter has been added to the application.

II. Response to Rejections

The rejections set out in the May 30 Office Action are summarized and addressed as follows.

(i) Rejections Under 35 U.S.C. §103(a).

a. Claims 14, 29, and 39 are rejected as allegedly obvious over Saido et al., *J. Biol. Chem.,* 269:15253-15257, 1994 ("Saido A") in view of Takeda Chem. Industries Ltd., EP 0 683 234 A1 ("Takeda"), Vigo-Pelfrey et al., *J. Neurochem.,* 61:1965-1968, 1993 ("Vigo-Pelfrey") and Goding, Monoclonal Antibodies, Academic Press Inc., pp. 56-97 (1983) ("Goding"). In response, without conceding the validity of the rejection, the claims have been amended to call for humanized, amyloid β-peptide free-end specific antibodies that bind specifically to a free N-terminus of soluble amyloid β-peptide or to a free C-terminus of soluble amyloid β peptide Aβ1-40.

The amended claims are not obvious over the prior art, either alone or in any combination. Saido A, the primary reference cited by the Examiner, discloses a purified fraction of polyclonal antibody 9204 ("purified polyclonal 9204"). Purified polyclonal 9204 differs from the antibodies called for in claims 14, 29 and 39 at least because purified polyclonal 9204 is not a

monoclonal antibody, is not a humanized antibody, and is not shown to bind Aβ that is soluble in CSF. Nor is there any suggestion in Saido A to modify purified polyclonal 9204 to arrive at the antibodies of claims 14, 29 and 39. Saido A is directed entirely to using antibodies as diagnostic tools in vitro, e.g., as probes in Western blotting or in the staining of tissue sections, where Aβ peptides are fixed to a solid substrate. Saido A provides no hint, reason or advantage to go through the time and expense to prepare a humanized antibody, because there would be no benefit or advantage in using a humanized antibody for the purposes set out in Saido A. Additionally, there is no advantage to modifying purified polyclonal 9204 to obtain an antibody that binds soluble Aβ, because the diagnostic in vitro assays set out in Saido A require antibody to bind denatured Aβ peptides. For at least these reasons, Saido A does not suggest the humanized, monoclonal antibodies of claims 14, 29 and 39.

Nor do the secondary references, either alone or in combination, provide any suggestion or reason to modify purified polyclonal 9204 to arrive at a humanized, free-end specific antibody that binds to soluble Aβ. As with Saido A, Takeda is directed to using anti-Aβ antibodies in diagnostic tests in vitro, e.g., "sandwich assays," to discriminate among different forms of Aβ. Takeda provides no hint that any benefit or advantage would result in preparing a humanized antibody for use in the Takeda sandwich assays. Nor does Takeda provide any suggestion or reason to provide an antibody that binds to Aβ that is soluble in CSF, as called for in claims 14, 29 and 39.

Nor does Vigo-Pelfrey or Goding cure the defects of Saido A. Vigo-Pelfrey merely discloses that CSF contains soluble Aβ. This fact is unexceptional and provides no reason, either alone or in combination with one or both of Saido A and/or Takeda to arrive at a humanized, free-end specific antibody that binds to soluble Aβ. Goding is merely cited generally for monoclonal antibodies.

In short, none of Saido A, Takeda, Vigo-Pelfrey, or Goding, either alone or in combination, provides any benefit or reason to arrive at a humanized, free-end specific antibody that binds to Aβ that is soluble in CSF. For at least these reasons, claims 14, 29 and 39 are not obvious over Saido A in view of Takeda, Vigo-Pelfrey and Goding and the rejection of claims 14, 29 and 39 as obvious over Saido A, Takeda, Vigo-Pelfrey and Goding should be withdrawn.

Other points raised by the Examiner in making the instant rejection are addressed as follows. The Examiner asserts that "Takeda et al[.] teach that their antibodies are useful for detecting amyloid beta in cerebrospinal fluid." *See* Office Action at page 4, second paragraph. This assertion is believed to be mistaken. The Examiner is respectfully invited to point out where Takeda discloses detecting amyloid beta in CSF. It is respectfully submitted that there is no such disclosure in Takeda. In the absence of such disclosure, the Examiner is requested to acknowledge in the next official action that Takeda fails to teach that their antibodies are useful for detecting Aβ in CSF.

The Examiner contends that one of ordinary skill in the art would have been motivated to make monoclonal antibodies to obtain an unlimited supply of high-affinity, high specificity antibody, to decrease lot to lot variability that can happen with polyclonal antisera and that Takeda teaches that monoclonal antibodies are useful for detection of Aβ1-40 and Aβ1-42 for the detection of Aβ species in vitro. To extent that these may or may not be general reasons to make monoclonal antibodies to be used in connection with in vitro diagnostic tests such as those disclosed in Saido A or Takeda, they provide no reason to expend the time and resources that would have been required to make humanized, monoclonal antibodies, as called for in the present claims. Accordingly, these asserted general reasons for making a monoclonal antibody do not provide a reason for modifying the prior art of record to arrive at the instant claims.

Lastly, the Examiner continues to mistakenly use the unremarkable fact that soluble Aβ is present in CSF as evidence that the antibodies disclosed in Saido A and/or Takeda bind to Aβ that is soluble in CSF. No such evidence exists. The antibodies disclosed in Saido A and Takeda were not raised against soluble Aβ and were never tested for binding to Aβ that is soluble in CSF. Nor were the diagnostic tests set out in Saido A and Takeda performed in situ. Thus, there is no basis for the Examiner to conclude that the antibodies disclosed in either of Saido A or Takeda do or do not bind to Aβ that is soluble in CSF.

In contrast to the prior art, the instant application sets forth the rationale to provide a humanized, free-end specific antibody that binds to Aβ that is soluble in CSF.

In *KSR International*, the Supreme Court set forth:

> [A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art. Although common sense directs one to look with care at a patent application that claims as innovation the combination of two known devices according to their established functions, it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does. This is so because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known.

KSR International Co. v. Teleflex Inc., 127 S. Ct. 1727, 1741 (2007).

In this instance, the prior art offers no reason that would have prompted a person of ordinary skill in the art to combine the prior art to arrive at a humanized, amyloid β-peptide free-end specific antibody that binds specifically to a free N-terminus of an amyloid β-peptide that is soluble in CSF or to a free C-terminus of amyloid β peptide Aβ1-40 that is soluble in CSF. The state of the art was such that to the extent it may have been possible to combine various elements of the prior art to arrive at such antibodies, the benefits to obtaining them were appreciated only in the context of discriminating among Aβ species in vitro. As set forth above, in this context one of ordinary skill in the art would find no reason or benefit for preparing a humanized antibody or an antibody that binds to Aβ that is soluble in CSF. The rationale for preparing a humanized, free-end specific antibody that binds to Aβ that is soluble in CSF, flows from the realization that such antibodies can be used as therapeutics to treat Alzheimer's disease, as set out in the instant application. The prior art cited by the Examiner fails to recognize the benefits of free-end specific antibodies to Aβ as therapeutics.

In contrast to the prior art, the instant specification provides the rationale for obtaining a humanized, amyloid β-peptide free-end specific antibody that binds specifically to a free N-terminus of an amyloid β-peptide that is soluble in CSF or to a free C-terminus of amyloid β peptide Aβ1-40 that is soluble in CSF. Thus, the instant specification sets forth the rationale for using antibodies as therapeutics for treatment of Alzheimer's disease, as follows:

> These soluble antisenilin-Aβ complexes are cleared from the central nervous system by drainage of the extracellular space, interstitial fluid and cerebrospinal fluid into the general blood circulation through the

> arachnoid villi of the superior sagittal sinus. In this manner, soluble Aβ peptides are prevented from accumulating in the extracellular space, interstitial fluid and cerebrospinal fluid to form amyloid deposits and/or to induce neurotoxicity. Furthermore, clearance of soluble amyloid-β peptides in accordance with the present invention is expected to reduce the inflammatory process observed in Alzheimer's Disease by inhibiting, for example, amyloid-β-induced complement activation and cytokine release, and block also the interaction of A β with cell surface receptors such as the RAGE receptor.

Specification at page 10, line 28 – page 11, line 4.

The application further provides the rationale for using free-end specific antibodies that discriminate between Aβ peptides and the APP precursor:

> As shown in Fig. 1 (see Schehr, 1994), and discussed in the Background Art section, the β- amyloid protein precursor (βAPP) is believed also to serve as a precursor for a proteolytic product, soluble β-amyloid protein precursor (sβAPP), thought to have growth promoting and neuroprotective functions. It will be readily appreciated by those of skill in the art that the stable expression of antisenilins in the central nervous system will not interfere with the normal biological functions of βAPP that are not associated with the formation of Aβ peptides

Specification at page 11, lines 10-19.

The specification further sets forth:

> [T]he antisenilin molecule, which is a recombinant antibody molecule containing the antigen-binding portion of a monoclonal antibody, is intended to encompass a chimeric or humanized immunoglobulin molecule of any isotype, as well as a single-chain antibody.

Specification at page 11, lines 24-28.

In short, it was the inventor of the instant application, not prior art, that appreciated that antibodies could be used as therapeutics to treat Alzheimer's disease, and that desirable properties of such antibodies included that they bind soluble Aβ in the CSF, be free end-specific such that they discriminate between Aβ and APP, and be humanized. In contrast, the state of the prior art was such that it envisioned antibodies that discriminated among different Aβ isoforms only in the context of in vitro diagnostics. Accordingly, in contrast to the instant application, the prior art provided no rationale, benefit or other reason to arrive at the claimed antibodies that are useful as

therapeutics for treatment of Alzheimer's disease. In the absence of any rationale, benefit or other reason to be found in the prior art, it is apparent that the Examiner has used the instant specification as a blue print to find the elements of the pending claims in the prior art and combine them as called for in the claims. Such hindsight reconstruction is impermissible. *In re Dow Chem. Co.,* 837, F.2d 469, 473 (Fed. Cir. 1983). For these reasons, additionally, claims 14, 29 and 39 are not obvious over the combination of Saido A, Takeda, Vigo-Pelfrey, and Goding.

In short, in contrast to the instant application, the references as a whole provide no problem to be solved and no benefit or other reason for making a humanized, amyloid β-peptide free-end specific antibody that binds specifically to a free N-terminus of amyloid β-peptide that is soluble in CSF or to a free C-terminus of amyloid β peptide Aβ1-40 that is soluble in CSF. The prior art thus provides no reason to combine elements as set forth by the Examiner to arrive at the antibody of claims 14, 29 and 39.

For all of the reasons set forth above, claims 14, 29 and 39 are not obvious over the combination of Saido A, Takeda, Vigo-Pelfrey, and Goding. Reconsideration of the claims and withdrawal of the rejection of claims 14, 29 and 39 over Saido A, Takeda, Vigo-Pelfrey, and Goding is requested.

b. Claims 14, 33 and 39 are rejected as allegedly obvious over Takeda Chem. Industries Ltd., EP 0 683 234 A1 ("Takeda"), Saido et al., *J. Biol. Chem.* 269:15253-15257 (1994) ("Saido A"), Saido et al., *J. Biol. Chem.* 268:25239-25243 (1993) ("Saido B"), Vigo-Pelfrey et al., J. Neurochem., 61:1965-1968, 1993 ("Vigo-Pelfrey") and Goding, Monoclonal Antibodies, Academic Press Inc., London pp. 56-97 (1983) ("Goding"). In response, without conceding the validity of the rejection, claims 14, 33 and 39 have been amended to call for humanized, amyloid β-peptide free-end specific antibodies that bind specifically to a free N-terminus of amyloid β-peptide that is soluble in CSF or to a free C-terminus of amyloid β peptide Aβ1-40 that is soluble in CSF. The prior art, taken as a whole, does not suggest the amended claims.

As a starting point for the instant rejection, the Examiner cites Takeda's antibody BA-27a. For the same reasons set forth immediately above in responding to the rejection based on Saido A, Takeda, Vigo-Pelfrey, and Goding, the prior art taken as a whole fails to provide any

reason to modify antibody BA-27a to arrive at a humanized, free-end specific antibody that binds specifically to the free C-terminus of amyloid β peptide Aβ1-40 that is soluble in CSF. Takeda discloses that BA-27a is useful to identify the Aβ1-40 isoform in vitro. There is no suggestion in Takeda that a humanized version of BA-27a would be useful as a therapeutic antibody. Takeda thus provides no benefit or reason to provide a humanized antibody that recognizes Aβ1-40 that is soluble in CSF, as called for in the present claims. Nor, for all of the reasons set forth above, do the secondary references cited by the Examiner, taken as whole, provide any benefit or rationale for modifying BA-27a to arrive at the pending claims.

For at least the reasons set forth above, claims 14, 33 and 39 are not obvious over Takeda in view of Saido A, Saido B, Vigo-Pelfrey, and Goding. Withdrawal of the rejection of claims 14, 33 and 39 over Takeda, Saido A, Saido B, Vigo-Pelfrey, and Goding is respectfully requested.

c. Claims 23, 35, 38 and 40 are rejected as allegedly obvious over combinations of Saido A, Takeda, Saido B, Vigo-Pelfrey and Goding, and in view further of Seubert et al., U.S. Patent No. 6,114,133 ("Seubert") and Duenas et al., *Bio Techniques* 16:476-483 (1994) ("Duenas"). In response, without conceding the validity of the rejection, claims 23, 35, 38 and 40 have been amended to call for humanized, single chain amyloid β-peptide free-end specific antibodies that bind specifically to a free N-terminus of amyloid β-peptide that is soluble in CSF or to a free C-terminus of amyloid β peptide Aβ1-40 that is soluble in CSF. The prior art, taken as a whole, does not suggest the amended claims.

As set forth above, claims 14, 29, 33 and 39 are not obvious over Saido A, Takeda, Saido B, Vigo-Pelfrey and Goding, at least because these references fail to provide any reason to arrive at a humanized, amyloid β-peptide free-end specific antibody that binds specifically to a free N-terminus of amyloid β-peptide that is soluble in CSF or to a free C-terminus of amyloid β peptide Aβ1-40 that is soluble in CSF, nor do they hint at any benefit or advantage that would arise from making a humanized antibody with these features. Claims 23, 35, 38 and 40 are likewise directed to a humanized, amyloid β-peptide free-end specific antibody that binds specifically to a free N-terminus of amyloid β-peptide that is soluble in CSF or to a free C-terminus of amyloid β peptide

Aβ1-40 that is soluble in CSF, with the additional feature that such antibodies are single chain antibodies. The arguments set forth for why claims 14, 29, 33 and 39 are not obvious over Saido A, Takeda, Saido B, Vigo-Pelfrey and Goding thus apply equally well to establish that claims 23, 35, 38 and 40 are not obvious over these references. The Examiner cites Seubert as disclosing Fv and other antibody fragments that bind Aβ are useful in detection techniques for use in screening or diagnostic assays and Duenas simply for single chain antibodies in general. Thus, neither Seubert nor Duenas, separately or in combination, provides any further reason to modify Saido A, Takeda, Saido B, Vigo-Pelfrey and Goding to arrive at a humanized, amyloid β-peptide free-end specific antibody that binds specifically to a free N-terminus of amyloid β-peptide that is soluble in CSF or to a free C-terminus of amyloid β peptide Aβ1-40 that is soluble in CSF. Thus, claims 23, 35, 38 and 40 are not obvious over any combination of Saido A, Takeda, Saido B, Vigo-Pelfrey, Goding, Seubert or Duenas.

For at least the reasons set forth above, the pending claims are not obvious over any combination of Saido A, Takeda, Saido B, Vigo-Pelfrey, Goding, Seubert or Duenas. Reconsideration of the claims and withdrawal of the instant rejection is requested.

(ii) Rejections Under 35 U.S.C. §112, paragraphs 1 and 2. Claims 39 and 40 are rejected for allegedly failing to comply with the written description requirement and for alleged indefiniteness. The rejections are based on the assertion that "an antibody that binds soluble beta amyloid cannot neutralize its neurotoxicity because it is not neurotoxic in the first place." *See* Office Action at page 16, first and last paragraphs. The rejections are respectfully traversed, on the grounds that the specification clearly sets forth that antibodies directed against soluble Aβ neutralize the neurotoxicity of Aβ, by inhibiting aggregation of Aβ peptides and/or blocking the interaction of Aβ with other molecules that contribute to the neurotoxicity of Aβ.

Thus, without being bound by theory, the specification sets forth at page 10, line 24-page 11, line 11:

> The secretion of antisenilins into the extracellular space, interstitial fluid and cerebrospinal fluid, where soluble Aβ peptides are present, promotes the formation of soluble antisenilin-Aβ complexes. These soluble antisenilin-Aβ complexes are cleared from the central nervous

> system by drainage of the extracellular space, interstitial fluid and cerebrospinal fluid into the general blood circulation through the arachnoid villi of the superior sagittal sinus. In this manner, soluble A Aβ peptides are prevented from accumulating in the extracellular space, interstitial fluid and cerebrospinal fluid to form amyloid deposits and/or to induce neurotoxicity (Fig. 1). Furthermore, clearance of soluble amyloid-Aβ peptides in accordance with the present invention is expected to reduce the inflammatory process observed in Alzheimer's Disease by inhibiting, for example, amyloid-Aβ-induced complement activation and cytokine release, and block also the interaction of Aβ with cell surface receptors such as the RAGE receptor.

The specification thus explicitly sets forth that neurotoxicity of soluble Aβ derives from accumulation of soluble Aβ into plaques and/or interaction of Aβ with cell surface receptors such as the RAGE receptor. Moreover, as set forth in the specification on page 6, Yan et al. (1996) provided data showing that Aβ bound to RAGE and triggered reactions that could generate cytotoxic oxidizing stimuli. It follows directly that antibodies that bind to soluble Aβ to inhibit its accumulation into plaques and/or interaction with cell surface receptors such as RAGE are "neutralizing" antibodies, as called for in claims 39 and 40. The basis for the rejections under 35 U.S.C. §112, paragraphs 1 and 2 is therefore not well taken. Reconsideration of claims 39 and 40 and withdrawal of the instant rejections is requested.

III. New Claims. New claims 41-57 have been added. The new claims are believed to be patentable over the prior art of record for at least the same reasons set forth in connection with claims 14, 23, 24, 33, 35, and 38-40. Additionally, the new claims are believed to meet all requirements for patentability set forth in sections 101 and 112.

It is noted that claims 41, 44, 47, 51 and 55 are directed to compositions comprising humanized, free-end specific antibodies that bind to Aβ that is soluble in CSF (as set forth respectively in claims 14, 23, 40, 50 and 54), claims 42, 45, 48, 52 and 56 are directed to such compositions further comprising a complex of the respective humanized, monoclonal antibodies and Aβ, and claims 43, 46, 49, 53 and 57 are directed to such compositions wherein the Aβ-peptide-antibody complexes are soluble. The prior art as a whole fails to suggest the compositions set forth

in claims 41-49 and 51-53 and 55-57. For these reason additionally, new claims 41-49 and 51-53 and 55-57are patentable over the prior art of record.

IV. Conclusion. Based on the preceding arguments and amendments, the subsisting claims are believed to be in condition for allowance and such action is earnestly solicited. If the Examiner believes that there are remaining issues that could be addressed by entry of an Examiner's Amendment, the Examiner is cordially invited to contact the undersigned attorney.

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